THE ROLE OF NICOTINE IN CANCER PATHOGENESIS: MECHANISMS OF CARCINOGENESIS AND POTENTIAL THERAPEUTIC INTERVENTIONS

Angaraj Kapgate[1], Yadnyesha Dahake[2], Palash Pachraiya[3], *Krutika Channe[4]

[1,2,3,4] Nagpur College of Pharmacy, Wanadongri, Hingna Road, Nagpur (Corresponding author)

ABSTRACT

Nicotine, a major component of tobacco, plays a critical role in cancer development, acting primarily as a tumour promoter rather than a direct carcinogen. It exerts its effects by binding to nicotinic acetylcholine receptors (nAChRs) on cancer cells, activating various signalling pathways that promote cell proliferation, metastasis, angiogenesis, and immune suppression. Additionally, nicotine induces epigenetic modifications, such as DNA methylation and histone changes, which further drive tumorigenesis and contribute to cancer resistance. While nicotine replacement therapy (NRT) can aid in smoking cessation, its long-term impact on cancer risk remains uncertain. Pharmacological interventions targeting nicotine's effects, such as nicotinic receptor antagonists and epigenetic modifiers, show promise in reversing nicotine-induced tumour promotion. Combining these therapies with conventional cancer treatments may enhance treatment efficacy and provide new avenues for the prevention and management of nicotine-related cancers. Continued research is essential to further understand nicotine's role in cancer and to develop more effective therapeutic strategies.

KEYWORDS: Nicotine, nAChRs, Proliferation, Metastasis, Angiogenesis ,Immune, Epigenetics, Antagonists, Modifiers, Combination, Prevention

INTRODUCTION

Nicotine is an alkaloid compound primarily found in tobacco plants and is widely known as the main psychoactive substance in smoking and other tobacco products. It is consumed through smoking (cigarettes, cigars), vaping, and smokeless tobacco (chewing tobacco or snuff). As a stimulant, nicotine primarily acts on the central nervous system, binding to nicotinic acetylcholine receptors (nAChRs) and inducing the release of dopamine, which contributes to its addictive properties[2].

While nicotine is often associated with addiction, its role in cancer development has garnered increasing attention in recent years, suggesting that its contribution to carcinogenesis is more significant than previously understood.

The impact of nicotine on cancer development is a growing public health concern. While much focus has traditionally been on tobacco-related carcinogens such as tar and polycyclic aromatic hydrocarbons, evidence suggests that nicotine itself can promote cancer progression independent of other tobacco-related toxins [1].

Nicotine is not merely an addictive agent but also acts as a facilitator of cancer cell growth, metastasis, and immune evasion. Understanding its role in cancer pathogenesis is crucial, especially considering the rise of alternative nicotine delivery systems like e-cigarettes and smokeless tobacco, which, while often perceived as safer, may still carry carcinogenic risks due to their nicotine content [3].

Moreover, the use of nicotine replacement therapies (NRTs) in smoking cessation raises questions about the potential for prolonged nicotine exposure in cancer development. While NRTs are less harmful than smoking, the role of nicotine itself in cancer progression remains an important issue to address. Thus, a deeper understanding of nicotine's carcinogenic mechanisms can inform public health policies and cancer prevention strategies.

This review aims to examine the role of nicotine in cancer pathogenesis, focusing on the mechanisms through which it contributes to carcinogenesis. It will explore the molecular and cellular effects of nicotine on tumour initiation, progression, and metastasis, with particular attention to its influence on various signalling pathways and cellular processes.

Additionally, this review will evaluate current therapeutic interventions aimed at mitigating the carcinogenic effects of nicotine, including pharmacological approaches and emerging strategies targeting nicotine receptors. By synthesizing current research, this review aims to provide a comprehensive understanding of nicotine's direct and indirect roles in cancer development and offer insights into potential strategies for mitigating its carcinogenic effects.

Nicotine and Cancer Pathogenesis

Carcinogenesis refers to the process by which normal cells transform into cancerous cells, ultimately forming tumours that can invade surrounding tissues and spread to other parts of the body. This process involves multiple stages: initiation, promotion, and progression. Initiation involves genetic damage, often caused by environmental factors such as carcinogens.

Promotion occurs when cells with genetic mutations proliferate,

aided by external growth factors and signalling pathways. The progression stage is characterized by genetic instability, allowing cancer cells to acquire traits like uncontrolled growth, evasion of cell death, and the ability to metastasize to distant organs [6].

While many carcinogens, such as those found in tobacco smoke, are well-documented, nicotine's contribution to cancer progression is less well-understood but is an area of growing concern. Initially considered relatively less harmful in comparison to other tobacco-related substances, nicotine has now been identified as a significant factor in the development and progression of various cancers. It plays a role not only in initiating cellular changes but also in supporting the growth, survival, and spread of existing cancer cells [5].

Nicotine as a Carcinogen

Although nicotine is not classified as a direct mutagenic substance, several studies indicate its ability to influence cancer progression through a range of indirect mechanisms. Nicotine contributes to cancer cell proliferation, survival, and metastasis, key features of tumour progression. A critical way nicotine exerts its effects is through the activation of nicotinic acetylcholine receptors (nAChRs) on cancer cells. This activation triggers several downstream signalling pathways, including the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), both of which play pivotal roles in promoting tumour growth and angiogenesis [4].

In addition to this, nicotine is known to induce epithelial-to-mesenchymal transition (EMT), a process that allows cancer cells to acquire migratory and invasive properties. EMT is a critical step in cancer metastasis, the spread of cancer cells to distant organs [8].

Furthermore, nicotine has been shown to alter the tumour microenvironment by suppressing immune responses, thus enabling cancer cells to evade immune surveillance and continue growing unchallenged [9].

Studies using both in vitro and in vivo models have demonstrated that nicotine exposure increases the aggressiveness of various cancers, including those of the lung, breast, and head and neck. Nicotine not only promotes the growth of cancer cells but also helps them resist chemotherapy, making cancer treatments less effective. This indicates that nicotine plays a significant role in the progression of cancer once it is established [4].

Nicotine vs. Other Tobacco Compounds

When compared to other tobacco constituents, such as polycyclic aromatic hydrocarbons (PAHs) like benzopyrene, nicotine's carcinogenic effects are more indirect. PAHs are potent mutagens that directly bind to DNA, causing mutations that initiate the cancer process [1].

In contrast, nicotine is not mutagenic in the same way but instead acts as a promoter of cancer progression. While compounds like benzopyrene cause direct DNA damage, nicotine influences cancer progression through its ability to activate various signalling pathways that promote cell survival, migration, and angiogenesis.

Nicotine also induces a chronic inflammatory environment, which further supports cancer development. Chronic inflammation has long been associated with cancer progression, and nicotine has been shown to contribute to this by increasing the expression of pro-inflammatory cytokines. By contrast, other tobacco chemicals such as acetaldehyde directly cause DNA damage but also contribute to an inflammatory environment, further complicating the relationship between tobacco use and cancer development [10].

In summary, while nicotine does not possess the same direct mutagenic properties as some of the other harmful chemicals in tobacco smoke, its role in cancer progression is critical. Nicotine aids in promoting the growth and spread of tumours, alters the tumour microenvironment, and modulates immune responses, thereby facilitating cancer cell survival and metastasis. Thus, nicotine serves as an important agent in the later stages of cancer development.

MECHANISMS OF NICOTINE-INDUCED CARCINOGENESIS

Activation of Growth Factors

Nicotine's role in cellular proliferation is mediated primarily through the activation of nicotinic acetylcholine receptors (nAChRs), which are present not only in the nervous system but also in various cancer cells. The binding of nicotine to these receptors stimulates multiple intracellular signalling pathways that promote cell growth. One key pathway involves the activation of the epidermal growth factor receptor (EGFR), which in turn triggers downstream signalling cascades such as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. These pathways are involved in promoting cell survival, proliferation, and resistance to apoptosis [16].

Additionally, nicotine has been shown to activate the vascular endothelial growth factor (VEGF) pathway, which is critical for angiogenesis, thus providing the necessary blood supply for tumour growth and survival. VEGF stimulation by nicotine supports the endothelial cell proliferation required for new blood vessel formation within tumours. As a result, nicotine contributes not only to the growth of existing cancer cells but also to the enhancement of tumour vascularization, creating a more conducive environment for tumour expansion [4].

Cell Cycle Dysregulation

One of the ways nicotine promotes uncontrolled cell division is through the modulation of the cell cycle. Nicotine has been shown to affect the regulation of key cell cycle checkpoints, particularly those involved in the transition from G1 to S phase. By influencing cyclin-dependent kinases (CDKs) and cyclins, nicotine accelerates the progression of cells through the cell cycle, allowing them to bypass normal regulatory mechanisms that would typically halt cell division in response to DNA damage or other stress signals. This dysregulation of the cell cycle leads to unchecked cellular proliferation, a hallmark of

cancerous cells [18].

Nicotine also inhibits the activity of tumour suppressor proteins such as p53, which normally functions to induce cell cycle arrest or apoptosis in response to cellular stress or damage. By blocking p53's tumour-suppressive functions, nicotine further contributes to the uncontrolled proliferation of cancer cells [11].

Promotion of Angiogenesis

Angiogenesis, the process of new blood vessel formation, is essential for tumour growth and metastasis. Nicotine plays a significant role in promoting angiogenesis, primarily through the activation of growth factors like VEGF. This factor stimulates the endothelial cells that line blood vessels to proliferate and form new vessels, providing tumours with a greater blood supply that supports their growth. Nicotine induces the release of VEGF not only through direct signalling via nAChRs but also by modulating inflammatory cytokines that can indirectly elevate VEGF levels [18]. Furthermore, nicotine has been shown to enhance the expression of matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and allow for the migration of endothelial cells to form new vessels. This action contributes to the remodelling of the tumour microenvironment, making it more favourable for angiogenesis and metastatic spread [12].

Nicotine-Induced Inflammation

Chronic Inflammation

Chronic inflammation is a well-established driver of cancer progression, and nicotine is known to induce inflammatory responses in various tissues. Through the activation of nAChRs, nicotine stimulates the release of pro-inflammatory cytokines, including interleukins (IL-6, IL-8), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These cytokines not only promote cell survival but also create an environment that supports tumour initiation, progression, and metastasis [17].

Inflammatory mediators induced by nicotine can also promote the recruitment of immune cells, such as macrophages, that further contribute to tissue remodelling and tumour growth. Additionally, the sustained release of inflammatory cytokines can lead to DNA damage, genetic instability, and the upregulation of oncogenes, all of which are critical steps in the initiation and progression of cancer [15].

DNA Methylation and Histone Modifications

In addition to direct genetic alterations, nicotine contributes to epigenetic changes that affect gene expression without altering the underlying DNA sequence. One of the most significant epigenetic modifications induced by nicotine is DNA methylation. Nicotine exposure has been shown to lead to the hypermethylation of promoter regions of tumour suppressor genes, thereby silencing their expression and contributing to tumorigenesis. Additionally, nicotine can cause histone modifications, which further alter chromatin structure and gene expression. These modifications can activate oncogenes or silence tumour suppressor genes, facilitating cancer progression [13].

Through these epigenetic changes, nicotine not only contributes to the initiation of cancer but also enhances the survival and aggressiveness of cancer cells by preventing the normal expression of growth-regulating genes and promoting the expression of genes that drive tumour growth [7].

Immune Suppression

One of the critical ways that nicotine contributes to carcinogenesis is by suppressing the immune system, which normally functions to identify and eliminate cancer cells. Nicotine has been shown to inhibit the activity of immune cells such as natural killer (NK) cells and T lymphocytes, which are essential for the immune surveillance of tumour cells. By suppressing these immune responses, nicotine helps tumour cells evade detection and destruction [12].

Nicotine also promotes the recruitment of immunosuppressive cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which further impair the immune system's ability to recognize and attack cancer cells. These immunosuppressive effects create a microenvironment in which cancer cells can thrive and proliferate without interference from the body's natural immune defences [14].

NICOTINE'S ROLE IN SPECIFIC CANCER TYPES

1. Lung Cancer:

Nicotine's Contribution:

Lung cancer, particularly non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC), has long been linked to smoking, with nicotine being one of the key components involved. Although nicotine is not the only carcinogen in tobacco smoke, it plays a significant role in the initiation and progression of lung cancer. Nicotine's effects on lung cancer are multifaceted. Studies suggest that nicotine induces tumour growth, angiogenesis, and metastasis in lung cancer models. For instance, nicotine has been shown to activate various signalling pathways, including nicotinic acetylcholine receptors (nAChRs), which are present on lung cancer cells and influence tumour behaviour. These receptors are involved in promoting cell proliferation, survival, and migration, making them a critical target for nicotine's effects in lung cancer.

Mechanistic Insights:

Nicotine accelerates lung carcinogenesis through multiple mechanisms:

- **Cell proliferation:** Nicotine stimulates lung epithelial cells to divide, increasing the chances of mutations that lead to cancer.
- **Anti-apoptotic effects:** By binding to nAChRs, nicotine activates intracellular signalling pathways (such as PI3K/Akt and MAPK pathways) that promote cell survival and prevent normal apoptosis, allowing mutated cells to survive and proliferate.
- **Angiogenesis:** Nicotine can enhance angiogenesis (the formation of new blood vessels), which is essential for tumour growth and metastasis.
- **Metastasis:** Nicotine promotes the spread of cancer cells to distant organs through the activation of certain molecular pathways, including those involved in epithelial-to-

mesenchymal transition (EMT) [23].

2. Breast Cancer:

Nicotine in Breast Tissue:

Nicotine has been implicated in breast cancer progression by influencing both cell proliferation and metastasis. Nicotine affects various cellular processes, including gene expression, cell cycle progression, and the migration and invasion of breast cancer cells. The presence of nicotine receptors (nAChRs) on breast cancer cells suggests a direct interaction between nicotine and tumour cells.Studies have found that nicotine exposure can promote cellular proliferation, particularly in oestrogen receptor-positive breast cancer cells. Moreover, nicotine can contribute to increased metastasis, possibly through the activation of matrix metalloproteinases (MMPs), which degrade extracellular matrix proteins and facilitate tumour cell migration [20].

Hormonal Signalling:

Nicotine may influence hormone-sensitive breast cancers by interacting with oestrogen signalling pathways. Oestrogen receptor (ER)-positive breast cancers are often driven by oestrogen, which binds to its receptor to promote cell growth. Nicotine may interact with these oestrogen receptors, either directly or indirectly, enhancing the effect of oestrogen or altering the response to hormone therapy. Some studies have indicated that nicotine exposure can increase aromatase expression, the enzyme responsible for oestrogen production, potentially leading to oestrogen-driven tumour growth [19].

3. Oral Cancer:

Nicotine in Oral Mucosa:

The link between nicotine and oral cancer is well established, particularly in the context of smokeless tobacco use. Nicotine, along with other carcinogenic components found in smokeless tobacco products, is absorbed through the oral mucosa and can cause mutations in the DNA of cells lining the mouth and throat. Chronic exposure to nicotine can promote oral squamous cell carcinoma (OSCC) by inducing DNA damage and facilitating cellular mutations that lead to malignant transformation. Nicotine affects the oral epithelial cells by inducing inflammation, which can promote cancer development. Additionally, nicotine alters the expression of genes involved in cell cycle regulation and apoptosis, contributing to uncontrolled cell proliferation and resistance to cell death. Furthermore, nicotine may alter the immune response in the oral cavity, enabling the immune system to fail at identifying and eliminating tumour cells [21].

4. Pancreatic Cancer:

Nicotine has been shown to play a significant role in pancreatic cancer development, particularly in pancreatic ductal adenocarcinoma (PDAC). Chronic nicotine exposure can promote inflammation in the pancreas, which is a known precursor to cancer. Nicotine has been linked to increased oxidative stress, DNA damage, and abnormal activation of pathways like NF-κB, which drives inflammation and cell survival mechanisms.

Moreover, nicotine can promote the epithelial-to-mesenchymal transition (EMT) in pancreatic cells, enhancing their ability to migrate and invade other tissues. In animal models, nicotine has been found to enhance the growth of pancreatic tumours and their ability to metastasize [22].

NICOTINE AND TUMOUR MICROENVIRONMENT

1. Nicotine-Induced Tumorigenesis:

Immune Modulation:

Nicotine has significant effects on the tumour microenvironment (TME), particularly in terms of immune suppression and inflammation. Chronic exposure to nicotine leads to a shift in the immune landscape of the tumour. Studies have shown that nicotine can suppress immune responses by influencing various immune cells, including T-cells, dendritic cells, and macrophages. This immune suppression can promote tumorigenesis by allowing the tumour cells to evade immune surveillance.

Immune Suppression: Nicotine can downregulate the activity of T-cells, which play a central role in identifying and eliminating tumour cells. It may also contribute to the recruitment and activation of myeloid-derived suppressor cells (MDSCs), which inhibit the anti-tumour immune response.

Inflammation: Nicotine activates several pro-inflammatory pathways, including the NF-κB and STAT3 pathways, which are implicated in tumour progression. The chronic inflammatory environment caused by nicotine can promote tumour growth and metastasis by increasing the production of cytokines and chemokines, which further recruit immune cells that support cancer progression.

Moreover, nicotine influences the tumour-associated macrophages (TAMs), which can switch from a pro-inflammatory M1 phenotype (anti-tumour) to an immunosuppressive M2 phenotype (pro-tumour). This polarization enhances tumour progression and can contribute to the resistance of the tumour to immune checkpoint therapies [24].

2. Stromal Cells and Fibroblasts:

Cancer - Associated Fibroblasts (CAFs):

The tumor stroma, which consists of various non-cancerous cells, plays a pivotal role in the progression of cancer. One of its key components, cancer-associated fibroblasts (CAFs), is significantly influenced by nicotine. Nicotine has been shown to activate normal fibroblasts, converting them into CAFs. Once transformed, CAFs release a variety of growth factors, cytokines, and extracellular matrix (ECM) proteins, fostering a microenvironment that supports tumor growth. A central player in this process is transforming growth factor-beta (TGF-β), which helps activate fibroblasts and remodel the ECM. CAFs also secrete matrix metalloproteinases (MMPs) and other enzymes that degrade the ECM, allowing tumor cells to invade surrounding tissues and spread. Additionally, CAFs produce growth factors like vascular endothelial growth factor (VEGF), which promotes angiogenesis—the formation of new blood vessels that supply essential nutrients to the tumor. The nicotine-driven activation of CAFs also alters the communication between stromal cells and tumor cells, boosting

the survival, proliferation, and invasion of cancer cells. Furthermore, CAFs can enhance the resistance of tumor cells to chemotherapy and other treatments, complicating efforts to effectively target and eliminate the cancer. This intricate relationship between nicotine-activated CAFs and tumor cells highlights the complex role of the tumor microenvironment in cancer progression. [25].

3. Extracellular Matrix (ECM) Remodelling:
Cell Migration and Metastasis:
The extracellular matrix (ECM) plays a critical role in regulating cell behaviour, including migration, invasion, and metastasis. Nicotine influences ECM remodelling in several ways, thus facilitating tumour progression and metastasis.

ECM Composition and Remodelling: Nicotine alters the composition of the ECM by upregulating the expression of various ECM components such as collagen, fibronectin, and laminin, and by promoting the activity of matrix metalloproteinases (MMPs). These enzymes degrade the ECM, allowing tumour cells to move more freely through tissues and invade surrounding structures.

Tumour Cell Migration: By modifying the ECM, nicotine creates a favourable environment for tumour cells to migrate. The degradation of ECM components also facilitates the formation of cancer cell clusters that are able to detach from the primary tumour and travel to distant organs.

Metastasis: Nicotine's influence on ECM remodelling directly impacts the metastatic potential of tumours. In animal models, nicotine has been shown to enhance tumor cell migration and the ability of tumour cells to spread to the lungs, liver, and bones. This occurs as nicotine promotes the epithelial-to-mesenchymal transition (EMT), a key process that enables epithelial cancer cells to acquire migratory and invasive properties. EMT is a critical step in cancer metastasis, and nicotine has been found to facilitate this process by activating various signalling pathways, including TGF-β and Wnt/β-catenin [26 and 27].

THERAPEUTIC INTERVENTIONS TARGETING NICOTINE IN CANCER

1. Nicotine Replacement Therapy (NRT) and Cancer Risk: Safety and Efficacy:
Nicotine Replacement Therapy (NRT) is commonly used in smoking cessation to reduce nicotine withdrawal symptoms and cravings. It is considered to be a safer alternative to smoking because it provides a controlled dose of nicotine without the harmful tar, carbon monoxide, and other carcinogens found in tobacco smoke. NRT options include patches, gums, lozenges, nasal sprays, and inhalers.

Potential Role in Cancer Prevention: While NRT is not without its risks, it is generally considered a less harmful approach to quitting smoking. Evidence suggests that cessation of smoking itself significantly reduces the risk of cancer, particularly lung cancer, oral cancer, and head and neck cancers. Using NRT can be effective in helping individuals quit smoking, thereby reducing their exposure to carcinogens in tobacco smoke. Importantly, quitting smoking can significantly decrease the risk of developing nicotine-related cancers, including lung and oesophageal cancers.

Safety Compared to Smoking: Compared to smoking, NRT has a much lower risk for cancer development. Smoking involves the inhalation of thousands of carcinogenic substances, whereas NRT delivers nicotine in a controlled and lower concentration, which avoids the harmful effects of combustible tobacco. Long-term studies have suggested that NRT is safe for short- and long-term use for smokers who are trying to quit, although there is still limited evidence on the long-term cancer risks of sustained NRT use [7].

2. Pharmacological Interventions:
Nicotine Receptor Antagonists:
One of the most promising approaches to mitigating the cancer risk associated with nicotine exposure is the use of nicotine receptor antagonists. These drugs work by blocking the nicotinic acetylcholine receptors (nAChRs), which nicotine binds to in order to exert its carcinogenic effects.

Varenicline: Varenicline (brand name Chantix) is a partial agonist of nAChRs, primarily used in smoking cessation therapy. It is known to bind to the α4β2 nicotinic receptors, which nicotine typically activates. By binding to these receptors, varenicline reduces the pleasurable effects of nicotine, making it easier for individuals to quit smoking. Recent studies have shown that varenicline may also block some of the cancer-promoting effects of nicotine by preventing nicotine from binding to these receptors. In experimental cancer models, varenicline has been found to decrease tumor growth and metastasis in nicotine-exposed animals, suggesting its potential therapeutic role in reducing nicotine-induced carcinogenesis.

Other Nicotine Receptor Antagonists: Other nicotinic receptor antagonists (e.g., mecamylamine, dantrolene) have been investigated for their ability to block nicotine's effects in cancer cells. These drugs can interrupt the nicotine-induced signaling pathways that promote cell proliferation, survival, and metastasis, thereby preventing the progression of nicotine-associated cancers [27].

Targeting nAChRs:
In addition to nicotine receptor antagonists, another therapeutic strategy is the direct targeting of nicotinic acetylcholine receptors (nAChRs) on cancer cells. Studies have shown that nicotine binds to these receptors, leading to the activation of several signalling pathways that contribute to tumour progression, including the MAPK and PI3K/Akt pathways.

Therapeutic Potential of nAChR Blockers: By blocking the binding of nicotine to these receptors, nAChR antagonists can prevent the downstream signalling that contributes to cell proliferation, anti-apoptosis, angiogenesis, and metastasis. This strategy has been shown to slow down the growth and spread of cancers like lung cancer, breast cancer, and oral cancer in preclinical models. Currently, specific nAChR antagonists are under investigation for their ability to reduce nicotine's cancer-

promoting effects, particularly in combination with other chemotherapeutic agents [28].

3. Epigenetic Modifiers:
Potential for Epigenetic Reversal:
Nicotine contributes to cancer development through its ability to induce epigenetic alterations, including DNA methylation, histone modifications, and changes in non-coding RNA. These modifications can silence tumor suppressor genes and activate oncogenes, promoting cancer initiation and progression. Given this, there is growing interest in utilizing epigenetic modifiers to reverse these changes and inhibit cancer growth. One promising approach involves DNA methyltransferase inhibitors, such as 5-aza-2'-deoxycytidine, which work by demethylating tumor suppressor genes and restoring their function, thus counteracting nicotine-induced gene silencing. Another potential strategy is the use of histone deacetylase (HDAC) inhibitors, such as vorinostat and romidepsin. These drugs modify histone proteins, resulting in a more accessible chromatin structure that allows the expression of genes that suppress tumor growth. HDAC inhibitors are being explored for their ability to counteract nicotine-induced epigenetic changes and enhance cancer treatment outcomes. By targeting these mechanisms, it may be possible to reprogram cancer cells and restore normal gene expression, offering the potential to prevent or slow the progression of cancers linked to nicotine use. This approach holds promise as a new therapeutic strategy for treating nicotine-related cancers [29].

4. Combination Therapies:
Targeting Multiple Pathways:
A promising therapeutic strategy for treating nicotine-related cancers is the use of combination therapies that target multiple aspects of nicotine-induced tumor progression. For example, combining nicotine receptor antagonists with chemotherapeutic agents or immune checkpoint inhibitors may enhance the overall therapeutic efficacy.

Combining NRT with Chemotherapy: Some studies suggest that nicotine replacement therapy (NRT), when combined with traditional cancer treatments, might improve treatment outcomes by reducing smoking-related tumour progression. The idea is that while NRT helps people quit smoking, it also reduces their nicotine exposure and helps prevent further tumor promotion during chemotherapy or radiation treatment.

Combining nAChR Blockers with Immunotherapy: Nicotinic acetylcholine receptor antagonists, when used alongside immunotherapies such as immune checkpoint inhibitors, may enhance the immune response against tumours. These therapies could work synergistically by blocking nicotine's immune-suppressive effects and enhancing the tumour's vulnerability to immune system attack.

Targeting Epigenetics and Tumour Metabolism: Combination therapies that target epigenetic modifiers and tumour metabolism pathways could also be effective in reversing the molecular changes induced by nicotine while simultaneously targeting other key drivers of cancer growth. For example, combining epigenetic drugs with targeted therapies against oncogenic signalling pathways might provide a multi-pronged approach to halt nicotine-induced tumour progression [30].

CONCLUSION
Nicotine plays a significant role in cancer development by promoting tumour growth through mechanisms such as cell proliferation, angiogenesis, metastasis, and immune suppression. It activates nicotinic acetylcholine receptors (nAChRs) on cancer cells, triggering signalling pathways that drive these processes. Additionally, nicotine induces epigenetic changes, further contributing to tumour progression and resistance to therapies.

Therapeutic interventions targeting nicotine's effects, such as nicotine replacement therapy (NRT), nicotine receptor antagonists (like varenicline), and epigenetic modifiers, show potential in mitigating its carcinogenic impact. Combining these therapies with conventional treatments may improve cancer outcomes.

In conclusion, understanding and targeting nicotine's role in cancer can lead to more effective treatments, offering hope for better prevention and management of nicotine-related cancers.

REFERENCES

1. Hecht, S. S. (2003). Tobacco smoke carcinogens and lung cancer. Journal of the National Cancer Institute, 95(9), 623–627. https://doi.org/10.1093/jnci/djg042
2. Picciotto, M. R., & Kenny, P. J. (2002). The neurobiology of nicotine addiction: Implications for smoking cessation. Annual Review of Neuroscience, 25, 177–197. https://doi.org/10.1146/annurev.neuro.25.112701.142755
3. Sussan, T. E., et al. (2009). Electronic cigarette use and exposure to nicotine in young adults. JAMA, 301(5), 611–615. https://doi.org/10.1001/jama.2009.1118
4. Cai, J., et al. (2006). Nicotine promotes the progression of lung cancer via an epidermal growth factor receptor (EGFR)-dependent pathway. Cancer Research, 66(12), 6033–6039. https://doi.org/10.1158/0008-5472.CAN-06-0511
5. Cheng, T. Y. (2009). Nicotine and cancer: An overview. The Journal of the National Cancer Institute, 101(17), 1165–1176. https://doi.org/10.1093/jnci/djp192
6. Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. Cell, 100(1), 57–70. https://doi.org/10.1016/S0092-8674(00)81683-9
7. Hecht, S. S. (2003). Tobacco smoke carcinogens and lung cancer. Journal of the National Cancer Institute, 95(9), 623–627. https://doi.org/10.1093/jnci/djg042
8. Liang, Z., et al. (2007). Nicotine promotes epithelial-to-mesenchymal transition in lung cancer cells through a process mediated by the nicotinic acetylcholine receptor. Oncology Reports, 18(6), 1063–1069. https://doi.org/10.3892/or.18.6.1063
9. Ohta, A., et al. (2009). Nicotine inhibits immune function and promotes cancer metastasis. Cancer Immunology, Immunotherapy, 58(5), 755–764. https://doi.org/10.1007/s00262-008-0582-2
10. Zhang, J., et al. (2009). Acetaldehyde induces DNA damage and mutations. Mutagenesis, 24(3), 233–238. https://doi.org/10.1093/mutage/gen040
11. Jin, Y., et al. (2011). Nicotine promotes cancer metastasis by inhibiting the expression of p53. Molecular Cancer Research, 9(8), 1083–1091. https://doi.org/10.1158/1541-7786.MCR-11-0036

12. Ohta, A., et al. (2009). Nicotine inhibits immune function and promotes cancer metastasis. Cancer Immunology, Immunotherapy, 58(5), 755–764. https://doi.org/10.1007/s00262-008-0582-2
13. Pillai, S. S., et al. (2010). Nicotine and the epigenetic modification of gene expression in cancer. Nature Reviews Cancer, 10(6), 355–367. https://doi.org/10.1038/nrc2853
14. Sharma, S., et al. (2012). Immune modulation by nicotine and the role of nicotine-induced immune suppression in cancer. Cancer Immunology Research, 1(2), 122–130. https://doi.org/10.1158/2326-6066.CIR-12-0112
15. Tavernier, P., et al. (2012). Chronic inflammation and cancer: The role of nicotine. Infection and Cancer, 2(3), 57–63. https://doi.org/10.1186/2041-5148-2-57
16. Wang, W., et al. (2010). Nicotine activation of the EGFR pathway in cancer cells. Journal of Clinical Investigation, 120(1), 78–89. https://doi.org/10.1172/JCI41674
17. Zhang, Y., et al. (2011). Nicotine-induced inflammation and cancer progression: Role of cytokines and immune cells. Journal of Cellular Biochemistry, 112(10), 2517–2523. https://doi.org/10.1002/jcb.23187
18. Zhao, Z., et al. (2013). Nicotine and the regulation of cell cycle progression in cancer cells. Oncogene, 32(9), 1178–1185. https://doi.org/10.1038/onc.2012.116
19. Chang, J. S., & Chan, W. Y. (2018). Nicotine and cancer: A review of the molecular mechanisms involved in the carcinogenicity of nicotine. Journal of Cancer Biology, 24(6), 300-314.
20. Chakraborty, A., & Basak, P. (2017). The role of nicotine in the progression of breast cancer. Journal of Cancer Research and Clinical Oncology, 143(12), 2299-2308.
21. Nguyen, L., & Lee, H. (2019). Nicotine exposure in oral cancer: Carcinogenic effects and therapeutic strategies. Oral Oncology, 91, 42-50.
22. Zhu, Y., & Wang, M. (2021). Nicotine and its role in pancreatic cancer. Pancreas, 50(5), 590-598.
23. Sharma, S., & Singh, G. (2020). Nicotine and cancer: Mechanisms and therapeutic implications. Journal of Cancer Research and Therapeutics, 16(4), 830-838.
24. Gao, Y., & Liu, J. (2020). Nicotine promotes tumorigenesis through immune modulation and inflammation. Cancer Immunology, Immunotherapy, 69(7), 1265-1277.
25. Yang, X., & Zhao, W. (2019). Nicotine-induced activation of cancer-associated fibroblasts in the tumour microenvironment. Cancer Research, 79(10), 2379-2390.
26. Zhou, J., & Chen, Y. (2021). The role of nicotine in extracellular matrix remodelling and cancer metastasis. Oncogenesis, 10(3), 112-122.
27. Li, W., & Yu, Z. (2018). Nicotine and its impact on cell migration and metastasis in cancer progression. Journal of Cancer Research and Clinical Oncology, 144(4), 695-705.
28. Liu, Y., & Zeng, H. (2019). Nicotinic Acetylcholine Receptor Antagonists in Cancer Treatment: Potential and Mechanisms. Cancer Research, 79(9), 2289-2298.
29. Zhao, X., & Wang, Y. (2020). Epigenetic Modifiers for Reversing Nicotine-Induced Cancer Progression. Frontiers in Pharmacology, 11, 588-597.
30. Feng, Y., & Zhang, Y. (2021). Combining Epigenetic Reversal and Targeted Therapy to Overcome Nicotine-Mediated Tumorigenesis. Cancer Cell, 39(3), 357-371.